REMARKS

Reconsideration of the rejections set forth in the Office action mailed December 31, 2002 is respectfully requested.

I. Amendments

Independent claim 1 has been amended to recite a method of "promoting" hematopoietic stem cell differentiation. Support is found in the specification at, for example, page 4, lines 20-21, page 18, lines 39-40, page 25, line 13, and page 27, lines 10-11. The claim is also amended to recite that contacting the cells with the antisense oligomer takes place *in vitro*, and to recite that the sequence of the oligomer is directed to a target sequence spanning the translational start codon or an intron or exon junction site of an mRNA transcribed from a human EVI-1 zinc finger gene. Accordingly, claims 2, 8 and 9 are cancelled.

Claim 6 is limited to the sequence SEQ ID NO: 1. Accordingly, claim 7 is cancelled.

Claim 10 is redrafted to recite an embodiment of the method of independent claim 1, in which the hematopoietic stem cells to be contacted with the antisense oligomer are provided by (a) obtaining a stem cell-containing population from a subject and (b) treating the population in a manner effective to enrich it for stem cells. New dependent claim 21 recites the further step of infusing the antisense-treated cells into the subject (page 19, lines 6-10 of specification; original claim 10).

Claims 11-16, dependent on claim 10, are substantively similar to claims 2-7, dependent on parent claim 1, and are thereby cancelled.

Claim 17 is amended to recite that the antisense morpholino oligomer is directed to a sequence spanning the mRNA translational start codon of a human EVI-1 zinc finger gene. New claim 22 specifies that the base sequence of the oligomer is SEQ ID NO: 1.

Claim 19 is amended to remove the term "substantially", and claim 20 is cancelled.

No new matter is added by any of the amendments.

II. Allowable Subject Matter

Claims 18 and 19 were found free of the prior art searched, as they pertain to elected sequence SEQ ID NO: 1.

III. Rejections under 35 U.S.C. §112, Second Paragraph

Claims 19 and 20 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the term "substantially uncharged backbone" was objected to. Claim 19 has been amended to remove the term "substantially", as noted above.

In view of the foregoing, the applicants submit that the amended claims comply with the requirements of 35 U.S.C. §112, second paragraph.

IV. Rejections under 35 U.S.C. §112, Second Paragraph

Claims 1-17 were rejected under 35 U.S.C. §112, second paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The claim language at issue pertained to targeting sequences directed to specified regions of "mRNA preferentially expressed in stem cells".

As discussed above, independent claim 19 and dependent claims 6 and 22 recite the sequence SEQ ID NO: 1. Independent claims 1 and 17 have been amended to recite that the morpholino oligomer targets the human EVI-1 zinc finger gene, at the translational start codon or an intron or exon junction site. One skilled in the art could readily envision, based on the disclosure, oligonucleotide sequences which "span[s] the translational start codon or an intron or exon junction site of an mRNA transcribed from a human EVI-1 zinc finger gene", based on the known human EVI-1 zinc finger gene sequence, which is cited at page 16, lines 14-15 of the specification.

In view of the foregoing, the applicants submit that the amended claims comply with the requirements of 35 U.S.C. §112, second paragraph.

V. Rejections under 35 U.S.C. §112, First Paragraph

Claims 1-16 and 20 were rejected under 35 U.S.C. §112, first paragraph, on the grounds that the specification, while being enabling for "decreasing the number of HPP-CFC following *in vitro* administration of an antisense oligonucleotide targeting the zinc finger protein EVI-1", does not enable a method of modulating stem cell differentiation *in vivo*, *in vitro* or *ex vivo*

comprising the administration of antisense targeting "any and/or all mRNA preferentially expressed in stem cells".

As noted above, independent claim 1 has been amended to recite a method of promoting stem cell differentiation *in vitro*, by employing an antisense oligomer targeting the zinc finger protein EVI-1, as stated by the Examiner. Applicants submit that "decreasing the number of HPP-CFC" relative to the number of clonogenic cells, as shown in Figure 3 and Table 2 (page 27) of the specification, is commensurate with "promoting differentiation" of the stem cells, as stated at page 27, lines 5-7 of the specification.

In accordance with claim 10, stem cells to be treated with antisense per the method of claim 1 can be obtained by enriching a cell population obtained from a subject. The antisense-treated stem cells may then be infused into the subject, as recited in claim 21.

The Examiner refers to "infusion of in vitro transfected cells" on page 6, line 13 of the Office Action (line 13). However, the method of the invention does not involve transfection of cells (i.e., the introduction of DNA into a recipient cell and its subsequent integration into the recipient cell's chromosomal DNA). Rather, the method involves contacting cells *in vitro* with a morpholino antisense oligomer, which is taken up into the cell and inhibits expression of a target mRNA, which is effective to promote differentiation of the stem cells *in vitro*, as shown in Example 2 of the specification.

As noted above, claim 20 has been cancelled.

In view of the foregoing, the applicants respectfully request that the rejections under 35 U.S.C. §112, first paragraph be withdrawn.

VI. Rejections under 35 U.S.C. §103

Claims 17 was rejected under 35 U.S.C. §103(a) as being unpatentable over Soreq *et al.* (WO 93/21202) in view of Baracchini *et al.* (U.S. Patent No. 5,801,154). The rejections are respectfully traversed in light of the following remarks.

A. The Invention

The applicant's invention, as embodied in claim 17, is directed to a composition comprising an antisense morpholino oligomer characterized by a backbone which is substantially uncharged,

and having the base sequence presented as SEQ ID NO:1.

B. The Cited Art

Baracchini *et al.* describe a large number of possible modifications that could be used in preparing an antisense oligomer (column 6 of patent). There is an emphasis on RNAse activation (column 8, lines 24-26), an activity which is not attributed to the claimed morpholino oligomers (see e.g. paragraph bridging pages 9-10 of applicants' specification). The oligomers exemplified in the Baracchini patent (see Tables 1-4) are phosphorothioate oligomers and phosphorothioate-phosphodiester mixed-backbone oligomers, all having fully charged backbones.

Soreq *et al.* discuss modulation of stem cell differentiation using phosphorothioated oligonucleotides directed to genes for proteins such as acetylcholinesterase (ACHE), cdc2 kinase, butyrylcholinesterase, and cdc2 homolog. There is no disclosure of morpholino oligomers or of an oligomer directed to an mRNA encoding a zinc finger gene.

C. Analysis

The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that the invention should be carried out and would have a reasonable likelihood of success, viewed in light of the prior art. Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure. *In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988).

In view of the large number of possible structural types disclosed in Baracchini, and the emphasis therein on charged-backbone oligonucleotide analogs and on RNAse activation, there is no motivation provided to use a substantially uncharged morpholino oligomer, as recited in claim 17; nor is there any suggestion of the benefits provided by such use.

Nor is there any suggestion in either reference to produce antisense oligomers targeted to an mRNA encoding a zinc finger gene.

Accordingly, the applicants respectfully request the Examiner to withdraw the rejections under 35 U.S.C. §103(a).

VII. Conclusion

In view of the foregoing, the applicant submits that the claims now pending are now in condition for allowance. A Notice of Allowance is, therefore, respectfully requested.

If in the opinion of the Examiner a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 838-4403.

Respectfully submitted,

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